JAMA Clinical Guidelines Synopsis

Treatment of *Helicobacter pylori* Infection

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GUIDELINE TITLE ACG Clinical Guideline: Treatment of *Helicobacter pylori* Infection

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PRIOR VERSION 2017

DEVELOPER American College of Gastroenterology (ACG)

TARGET POPULATION Outpatients aged 18 years or older with *H pylori* infection, with recommendations prioritized for persons residing in North America

SELECTED RECOMMENDATIONS

- For treatment-naive patients with *H pylori* infection, bismuth quadruple therapy (BQT) for 14 days is recommended as first-line treatment (strong recommendation; moderate quality of evidence [QOE]). When BQT is not an option, rifabutin triple therapy (conditional recommendation; low QOE) or potassium-competitive acid blocker (PCAB; eg, vonoprazan) dual therapy (conditional recommendation; moderate QOE) are suggested.
- For treatment-naive patients with *H pylori*, empirical use of regimens containing clarithromycin is not recommended. However, if no first-line treatment is available, PCAB triple therapy is suggested over proton pump inhibitor (PPI) triple therapy (conditional recommendation; moderate QOE).
- For patients with persistent *H pylori* infection who received PPI triple therapy rather than BQT, BQT is suggested (conditional recommendation; low QOE).
- For patients with persistent *H pylori* infection who have received BQT, rifabutin triple therapy is suggested (conditional recommendation; low QOE).

Summary of the Clinical Problem

Helicobacter pylori is a gram-negative bacterium that infects the stomach and can cause chronic gastritis, peptic ulcers, and gastric cancer.[1] New treatment regimens (**Table**) address increasing antibiotic resistance, incorporating antibiotic options such as rifabutin or more potent gastric acid–suppressing agents with a PCAB such as vonoprazan.[2]

Supplemental content

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Characteristics of the Guideline Source

Guideline panel members were composed of gastroenterologists and GRADE methodologists (eTable in the Supplement) who assessed eradication rate, treatment adherence, and adverse events. Certainty of evidence was rated as high, moderate, low, or very low based on confidence of the effect estimate. Strength of recommendation was rated as strong (recommended) or conditional (suggested) based on the balance of benefits and risks. Although *H pylori* infection affects people worldwide, the current guideline prioritized studies to provide advice for treatment-naive and treatment-experienced patients residing in North America.

Evidence Base

Of the 11 recommendations, 5 were for treatment-naive patients (1 strong recommendation based on moderate QOE; the remaining 4 conditional recommendations based on either low or moderate QOE), and 6 were for patients previously receiving treatment (all conditional recommendations based on either low or very low QOE). The guideline did not address diagnostic testing because the recommendations have not changed from prior guidelines.[1]

BQT is strongly recommended as first-line treatment for *H pylori* infection in treatment-naive patients (Table). The highest tolerated doses of each of the component therapies of BQT are preferred to improve the likelihood of *H pylori* eradication. Suboptimal regimens are those with duration shorter than 10 days, metronidazole less than 1.5 to 2.0 g/d, doxycycline substituted for tetracycline,[3] or PPIs at less than standard dose.[2] Several randomized clinical trials (RCTs) comparing BQT with PPI triple therapy demonstrated noninferiority or superiority of BQT.[4] A network meta-analysis of 68 RCTs (92 paired comparisons with 22 975 patients) demonstrated superiority of BQT, with an 81.3% eradication rate vs 75.7% for PPI triple

Table. Recommended Regimens for Treatment-Naive Patients With *Helicobacter pylori* Infection

Regimen	Drug (dosage)
BQT	PPI (standard dose) twice daily[a]; bismuth subcitrate (120-300 mg) or subsalicylate (300 mg) 4 times daily; tetracycline (500 mg) 4 times daily; and metronidazole (500 mg) 3 or 4 times daily for 14 d[b]
Rifabutin triple therapy	Omeprazole (40 mg), amoxicillin (1000 mg), and rifabutin (50 mg) 3 times daily for 14 d
PCAB dual therapy	Vonoprazan (20 mg twice daily) and amoxicillin (1000 mg 3 times daily) for 14 d
PCAB triple therapy	Vonoprazan (20 mg), clarithromycin (500 mg), and amoxicillin (1000 mg) twice daily for 14 d
PPI triple therapy	PPI (standard dose), clarithromycin (500 mg), and amoxicillin (1000 mg) twice daily for 14 d

Abbreviations: BQT, bismuth quadruple therapy; PCAB, potassium-competitive acid blocker; PPI, proton pump inhibitor.

[a] No specific PPI is suggested over others. However, as omeprazole, lansoprazole, and pantoprazole are extensively metabolized by CYP2C19, use of esomeprazole, rabeprazole, or a PCAB is recommended for patients who are known rapid or ultrarapid CYP2C19 metabolizers. Testing for the sole purpose of PPI selection is not recommended.

[b] Pylera (AbbVie Pharmaceuticals) is a combination preparation containing bismuth subcitrate, metronidazole, and tetracycline that is US Food and Drug Administration approved when combined with omeprazole. This regimen is dispensed as a 10-day regimen; however, the guideline recommends 14 days of optimized BQT due to higher eradication rates vs a 10-day duration.[10]

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therapy (odds ratio, 1.47; 95% CI, 1.02-2.11).[5] Although minor adverse events were common with BQT, rates of discontinuation were similar between the 2 treatment regimens in multiple studies.[2]

Rifabutin triple therapy or PCAB dual therapy are alternative first-line treatment options suggested for treatment-naive patients when BQT is not a viable option. Only 1 RCT studied rifabutin triple therapy as a first-line treatment, which was superior to dual therapy with amoxicillin-omeprazole, with an eradication rate of 83.8% vs 57.7% (mean difference, 26.1%; 95% CI, 18%-34.1%; $P < .001$).[6] No RCTs directly compared rifabutin triple therapy with PPI triple therapy or BQT as first-line therapy. In an RCT of 1046 patients in the US and Europe comprising 3 groups (open-label PCAB dual, double-blind PCAB triple, and double-blind PPI triple therapy), PCAB dual therapy was noninferior to PCAB triple therapy (eradication rates of 78.5% vs 78.8%; mean difference, −0.3%; 95% CI, −7.4% to 6.8%; $P = .007$ for noninferiority).[7] In a subgroup analysis of patients with clarithromycin-sensitive strains of *H pylori*, PCAB triple therapy was noninferior to PPI triple therapy in patients with clarithromycin-sensitive *H pylori* strains and superior in a subgroup analysis of clarithromycin-resistant strains (eradication rates of 65.8% vs 31.9%; mean difference, 33.9%; 95% CI, 17.7%-48.1%; $P < .001$).[7] Thus, PCAB triple therapy is suggested over PPI triple therapy for treatment-naive patients with unknown clarithromycin susceptibility and no available alternative first-line treatment options.

Test of cure with a urea breath test, fecal antigen test, or biopsy-based test at least 4 weeks after completion of therapy is a key concept based on expert opinion and is suggested for all patients treated for *H pylori*.[2] For treated patients with persistent infection who did not previously receive BQT, salvage therapy with BQT is recommended. For patients who received an initial course of BQT, rifabutin triple therapy is suggested. One RCT directly compared rifabutin triple therapy with BQT for salvage therapy in 364 patients with persistent *H pylori* infection who had received 2 prior treatment courses without use of BQT.[8] Rifabutin triple therapy was noninferior to BQT, with eradication rates of 89.0% vs 89.6% (mean difference, −0.6%; 95% CI, −7.1% to 5.9%; $P = .001$ for noninferiority); compared with BQT, the rate of total adverse events was lower with rifabutin triple therapy (26.4% vs 54.4%; $P < .001$) and adherence was higher (96.2% vs 85.4%; $P = .001$).

An RCT of 48 patients with persistent *H pylori* infection despite 1 previous course of treatment evaluated 14-day BQT vs PPI triple therapy and reported no statistically significant difference in eradication rates (75% vs 71%, respectively; $P = .78$), although lower-than-typical doses of metronidazole and tetracycline were used in the BQT regimen.[9] Given the potential risks of antibiotic resistance in patients previously treated with regimens containing clarithromycin or levofloxacin, BQT with the highest recommended doses of each component is suggested.

Benefits and Harms

Successful *H pylori* treatment regimens optimize eradication rates, thereby reducing complications of chronic *H pylori* infection such as gastric cancer, and reduce rates of adverse events and development of antibiotic-resistant organisms. Treatment regimens, including US Food and Drug Administration (FDA)–approved combinations and newer medications such as vonoprazan, are expensive, and the FDA has not approved BQT regimens prescribed separately in their 4 components.

Discussion

Among available options for treatment-naive patients with *H pylori* infection, BQT has the strongest evidence, can be safely given to patients with a penicillin allergy, and is first-line treatment. There is a dearth of evidence comparing alternative recommended regimens directly with BQT; supporting evidence is primarily derived from noninferiority studies or comparisons with regimens other than BQT. Thus, construction of hierarchical treatment recommendations for treatment-naive and treatment-experienced patients is difficult. For patients with persistent *H pylori* infection, regimens should be guided by prior treatment. Antibiotic susceptibility testing in *H pylori* treatment is an ongoing area of research, especially with increasing rates of clarithromycin resistance. However, there is limited evidence for routine antibiotic susceptibility testing vs empirical treatment with BQT, and current use is uncommon in clinical practice due to cost and logistical barriers.[10] Antibiotic susceptibility testing, if available, may be considered for patients with persistent *H pylori* infection despite multiple treatment courses or if a clarithromycin-containing regimen is being considered. The guideline recommendations prioritized studies performed in North America, so they may not generalize globally, where antibiotic resistance patterns may differ.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: None reported.

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